able cell products. On that basis, we believe the approach that we have chosen to be effective.

Discussion

Richard D. Weisel *(Toronto, Canada).* I greatly appreciate the excellent presentation, and I thank Drs Steinhoff and Stamm for sending me the manuscript in advance.

This study is important for cardiac surgeons because it echoes the information I presented last year suggesting that surgeons not only need to bypass coronary arteries, fix ventricles, and repair valves but also need to change the response of the heart to our interventions. Surgeons should introduce biologic interventions whenever they perform mechanical interventions. Your study demonstrates that biologic interventions can have profound effects of the response of the heart to our mechanical interventions. Unfortunately, you have not identified the mechanisms responsible for the benefit, and we therefore may have difficulty integrating this approach into our surgical practice.

When we originally implanted cells into the heart, we thought we were producing new heart cells. Subsequent studies have determined that none of the cells implanted into the heart transdifferentiated into new heart cells. The mechanism responsible for the improved function seen after the implantation of a variety of cell types has thus not been elucidated. How does cellular transplantation work? We have previously demonstrated that cellular transplantation induces angiogenesis and matrix remodeling, as well as recruiting endogenous stem cells from the heart and the bone marrow to the heart. If these are the mechanisms responsible for the improved function, then perhaps we need to augment those effects with any surgical interventions on the heart. So my first question for you is as follows: What is the mechanism responsible for the functional benefit, and should you augment your cells with genes or proteins to increase the benefit of cellular transplantation? Do you believe that your cells will transdifferentiate into cardiomyocytes?

I also had some concerns with your study. You had difficulty with the randomization. You were unable to complete the study according to your original trial design because of the unavailability of the room to perform the bone marrow biopsy. I am therefore concerned that you may have biased the randomization.

In your article, you report a significant difference between the two groups in end-systolic volume. I was concerned that the control group, the CABG alone group, had larger hearts before the operation and that this could not be improved with any type of therapy. Only 6 of your control patients had improvement postoperatively and 14 did not, which is not what we would anticipate after CABG. In addition, you did not use the Canadian laser in your control group. The Canadian laser is the insertion of a needle into the heart, which previous investigators have demonstrated to increase angiogenesis. The needle injection itself may have improved the functional outcome, and this procedure was only used in the cell transplant group, not the control group. I suggest that you use needle injection in your proposed phase III trial.

Finally, I was concerned about the randomization, because only 2 additional patients showed an improvement in LVEF in the treatment versus the control groups. The LVEF increased in 8 treated patients and 6 control patients. This difference was small but statistically significant. The difficulty you had with randomization thus could have influenced the outcomes.

In summary, I think that this is an important study, and it certainly will advance the field. Cardiac surgeons should go on to the next phase to develop a new treatment to restore cardiac function in our patients undergoing CABG. We should establish the mechanisms responsible for the improved function, however, but then augment those effects by adding genes or proteins to the cells implanted into the infarcted myocardium. Biologic interventions may be as important as mechanical treatments to restore our patients to full activity.

Dr. Steinhoff. Thank you, Dr. Weisel. The introduction of such a method has several phases, and this first phase I and II study of CD133+ intramyocardial stem cell transplantation is testing safety, and biological effects. Of course, the last is a difficult option with the diagnostic methods we have available. To unravel the underlying mechanisms there has to be a high correspondence between experimental models and clinical studies. I think it is difficult, at present, to exactly understand the sequence of cellular reactions that lead to cardiac regenerative processes.

We just had the basic science lecture about apoptosis, and apoptosis is also probably an important feature of exchange of cells necessary for tissue regeneration. So I think the addition of anti-apoptotic substances such as genes may be important; we have done research in anti-apoptotic gene transfer with stem cells and found a higher therapeutic effect in experimental models. Or proteins may be added. There are a number of candidate proteins that can improve stem cell function in the heart, which may lead the next clinical introductory phase. However, we have to learn step-by-step how stem cells can be used in cardiac therapy, what therapeutic effects they have, whether they are safe, whether or not they have side effects, how we can apply them, and in what disease condition.

In our study, we tried to find such a clinical therapeutic window treating chronic ischemia with intramyocardial injection of autologous CD133+ stem cells as an adjunct to a conventional CABG procedure. Of course, we are well aware of the weak points of our data. As you mentioned, we do not have a sham needle injection in the control group. We also had to overcome logistic problems in the prospective randomization of patients considering the bone marrow stem cell harvest and cell isolation methods. As compared to controls, however, we have seen in 35 patients treated with stem cells a consistent improvement in cardiac function—as great as 27% and with a mean of 10%—and I think that is really impressive. The lack of side effects is giving us confidence to go to the next clinical phase III study and to extend the experience. There are, of course, continuing improvements in isolation methods and conditioning of cells.

With respect to your mention of the control group, I agree that sham needle injection would be needed, and a next controlled study should include that. Also, a double-blinded study, as here it is only a single-blinded study, will be necessary to give the hard data needed for clinical introduction. Of course, this will take some time, but I am positive that we have good prospects for cardiac stem cell therapy in chronic ischemic heart disease.